General

Guideline Title

The role of neuropathology in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline.

Bibliographic Source(s)

Cahill DP, Sloan AE, Nahed BV, Aldape KD, Louis DN, Ryken TC, Kalkanis SN, Olson JJ. The role of neuropathology in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):531-49. [98 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Target Population

Adult patients (age ≥18 years) who have suspected low grade diffuse glioma.

Question

What are the optimal neuropathological techniques to diagnose low grade diffuse glioma in the adult?

Recommendations

- *Level I.* Histopathological analysis of a representative surgical sample of the lesion should be used to provide the diagnosis of low grade diffuse glioma.
- *Level III.* Both frozen section and cytopathologic/smear evaluation should be used to aid the intra-operative assessment of low grade diffuse glioma diagnosis. A resection specimen is preferred over a biopsy specimen, to minimize the potential for sampling error issues.

Target Population

Patients with histologically proven World Health Organization (WHO) grade II diffuse glioma.

Question

In adult patients (age ≥18 years) with histologically-proven WHO grade II diffuse glioma, is testing for IDH1 mutation (R132H and/or others) warranted? If so, is there a preferred method?

Recommendation

Level II. IDH gene mutation assessment, via IDH1 R132H antibody and/or IDH1/2 mutation hotspot sequencing, is highly-specific for low grade diffuse glioma, and is recommended as an additional test for classification and prognosis.

Target Population

Patients with histologically proven WHO grade II diffuse glioma.

Question

In adult patients (age ≥18 years) with histologically proven WHO grade II diffuse glioma, is testing for 1p/19q loss warranted? If so, is there a preferred method?

Recommendation

Level III. 1p/19q loss-of-heterozygosity testing, by fluorescence in situ hybridization (FISH), array-comparative genomic hybridization (CGH) or polymerase chain reaction (PCR), is recommended as an additional test in oligodendroglial cases for prognosis and potential treatment planning.

Target Population

Patients with histologically proven WHO grade II diffuse glioma.

Question

In adult patients (age ≥18 years) with histologically proven WHO grade II diffuse glioma, is methyl-guanine methyl-transferase (MGMT) promoter methylation testing warranted? If so, is there a preferred method?

Recommendation

There is insufficient evidence to recommend MGMT promoter methylation testing as a routine for low grade diffuse gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess the value of this and related markers for this target population.

Target Population

Patients with histologically proven WHO grade II diffuse glioma.

Question

In adult patients (age ≥18 years) with histologically proven WHO grade II diffuse glioma, is Ki-67/MIB1 immunohistochemistry warranted? If so, is there a preferred method to quantitate results?

Recommendation

Level III. Ki67/MIB1 immunohistochemistry is recommended as an option for prognostic assessment.

Definitions

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of Recommendation on Diagnosis

Class I evidence/Level I (or A) recommendation	Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class II	Evidence provided by one or more well-designed clinical studies of a *restricted* population using a "gold standard"

evidence/Level II (or B) recommendation	reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class III evidence/Level III (or C) recommendation	Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios

AANS/CNS Classification of Evidence and Levels of Recommendation on Clinical Assessments

Class I evidence/Level I recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a Kappa statistic >0.60
Class II evidence/Level II recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a Kappa statistic >0.40
Class III evidence/Level III recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a Kappa statistic <0.40

AANS/CNS Classification of Evidence and Levels of Recommendation on Prognosis

In order to evaluate papers addressing prognosis, five technical criteria are applied:

- Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
- Was patient follow-up sufficiently long and complete?
- Were objective outcome criteria applied in a "blinded" fashion?
- If subgroups with different prognoses were identified, was there adjustment for important prognostic factors?
- If specific prognostic factors were identified, was there validation in an independent "test set" group of patients?

Class I evidence/Level I recommendation: All five technical criteria above are satisfied.

Class II evidence/Level II recommendation: Four of five technical criteria are satisfied.

Class III evidence/Level III recommendation: Everything else.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diffuse low grade glioma

Guideline Category

Diagnosis

Evaluation

Management

Clinical Specialty

Neurology

Oncology

Pathology

Intended Users

Physicians

Guideline Objective(s)

To review the existing and emerging literature regarding the neuropathological diagnosis of low-grade diffuse glioma, with an assessment of the reliability of histopathological diagnosis in different scenarios, and the role (if any) of emerging molecular diagnostic techniques for these tumors

Target Population

Adult patients (age ≥18 years) who have suspected low grade diffuse glioma or histologically proven World Health Organization (WHO) grade II diffuse glioma

Interventions and Practices Considered

Neuropathological techniques to diagnose low-grade diffuse glioma

- Histopathological analysis
- Frozen section
- Cytopathologic/smear evaluation

Testing for *IDH1* mutation (IDH1 R132H antibody and/or IDH1/2 mutation hotspot sequencing)

Testing for 1p/19q loss (fluorescent in situ hybridization [FISH], array comparative genomic hybridization [CGH], polymerase chain reaction [PCR])

Methyl-guanine methyl-transferase (MGMT) promoter methylation testing (insufficient evidence to recommend)

Ki-67/MIB-1 immunohistochemistry

Major Outcomes Considered

- Overall survival
- Progression-free survival
- Sensitivity, specificity of diagnostic applications

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Examination Approach

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of low grade gliomas. The MEDLINE and EMBASE electronic databases were searched from 1990 through 2012, with additional data being gleaned from the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, and Cochrane Database of Abstracts of Reviews of Effects. The search strategies used a combination of subheadings and text words with the specifics of this work being outlined in each guideline section. Reference lists of the publications chosen for full text review were also screened for potentially relevant studies.

Study Selection

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the writing group. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more in depth information available. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Specific Search Strategy for This Guideline

The authors searched the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from 1983 to 2011 using the following search terms: "glioma AND pathology", "oligodendroglioma AND pathology", "astrocytoma AND pathology", "LGG AND pathology", "glioma AND diagnosis", "oligodendroglioma AND diagnosis", "astrocytoma AND diagnosis", "LGG AND diagnosis". This resulted in the identification of 262 unique articles, 10 of which met eligibility criteria (below). In addition, they performed PubMed searches of the National Library of Medicine database 1/1/1990–12/31/2012, using the following terms: "low-grade [All Fields] AND ("glioma"[MeSH Terms] OR "glioma"[All Fields]) AND ("pathology" [Subheading] OR "pathology"[All Fields] OR "pathology" [MeSH Terms])". This resulted in 2208 articles, which were reviewed yielding 163 potentially eligible articles. Links to "related articles" from highly relevant studies were utilized to broaden the search. Articles were also identified from the reference lists from references uncovered in initial searches. The references from prior evidence-based reports on low-grade diffuse and malignant glioma were also analyzed.

Study Selection

Inclusion criteria for literature included studies on low-grade diffuse gliomas (defined as astrocytomas, oligodendrogliomas and oligo-astrocytomas) in populations of patients 18 years and older. The authors excluded articles due to primary focus on higher-grade glioma (i.e., anaplastic gliomas and glioblastomas), optic glioma or pilocytic astrocytoma, non-English language, pediatric patients, trials of therapy, case-reports or small (<5) patient cohorts, and papers where data reported on high grade gliomas and low-grade diffuse gliomas could not be separated in the analysis.

Reviewers evaluated citation abstracts using the above a priori criteria for relevance. The same methodology was used for full-text screening of potentially relevant papers.

Number of Source Documents

A total of 2208 articles were identified, and after applying inclusion/exclusion criteria and removal of duplicates, 163 articles were deemed relevant. Two task force members independently reviewed the 163 "potentially" eligible articles, selecting 34 articles that were used to support the guideline recommendations.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of

Recommendation on Diagnosis

Class I evidence/Level I (or A) recommendation	Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
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AANS/CNS Classification of Evidence and Levels of Recommendation on Prognosis

In order to evaluate papers addressing prognosis, five technical criteria are applied:

- Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
- Was patient follow-up sufficiently long and complete?
- Were objective outcome criteria applied in a "blinded" fashion?
- If subgroups with different prognoses were identified, was there adjustment for important prognostic factors?
- If specific prognostic factors were identified, was there validation in an independent "test set" group of patients?

Class I evidence/Level I recommendation: All five technical criteria above are satisfied.

Class II evidence/Level II recommendation: Four of five technical criteria are satisfied.

Class III evidence/Level III recommendation: Everything else.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Evidence Analysis

Quality Assessment and Statistical Methods

Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Studies which met the eligibility criteria were subject to more detailed scrutiny and had their data extracted by one reviewer and the extracted

information was checked by one or more other reviewers. Evidence and summary tables, reporting the extracted study information and evidence classification, were generated for all of the included studies for each of the questions. Evidence tables were created with most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class and conclusion. The authors were directed to craft the data in the tables in a succinct and fact filled manner so as to allow for understanding of the literature entry. The literature in the evidence tables was expanded upon in the scientific foundation of each section so as to emphasize important points supporting its classification and contribution to recommendations. The method by which this was accomplished is expanded upon in the Joint Guideline Committee Guideline Development Methodology document (see the "Availability of Companion Documents" field). Internal drafts of the tables and manuscripts were developed by sharing between writers electronically, by telephone and meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent.

Specific Evidence Analysis for This Guideline

Quality Assessment

Studies which met the eligibility criteria were data extracted by one reviewer and the extracted information was checked by additional reviewers.

Evidence Classification and Recommendation Levels

Both the quality of the evidence and the strength of the recommendations for the diagnostic and prognostic data included here were graded according to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee (JGC) criteria (see the "Rating Scheme for the Strength of the Evidence" field). In order to evaluate papers addressing diagnostic accuracy, inter-observer variability, and prognosis, technical criteria were applied. These tables, specified as the scientific foundation evolves, provide detail on data classification on literature related to diagnostic accuracy, interobserver variability and prognosis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Panel Development

Recognizing the serious nature of low grade gliomas along with the lack of consensus among various treatment options, the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management and treatment of low grade glioma patients. The objectives of these guidelines are to establish the best evidence-based management of low grade gliomas in terms of imaging diagnosis, use of surgical biopsy and resection, assessment of tumor pathology, administration of systemic chemotherapy, and administration of radiation therapy. Because these tumors dependably recur or progress despite standard therapy, the Joint Tumor Section also recommended an evidence-based guideline be developed for progressive low grade gliomas and that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead writers of each section. These writers, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. Writers were provided training on the method of guideline development as used in this guideline set by written methods and instructions. The senior authors and CNS Guidelines Manager then worked with them on a step by step basis to confirm that the methods were followed as the literature was collected, assessed and documents developed. When writers were approached and preliminarily agreed to participate they were asked to complete a formal conflict of interest questionnaire confirming the appropriateness of their participation. At that point they also agreed to report any new conflicts of interest that might develop during the writing process. In this manner a multidisciplinary panel of writers referred to as the Low Grade Glioma Guidelines Task Force was assembled, with significant administrative, logistical and analytical support from the national CNS Guidelines Committee. The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

Topic Range of This Systematic Review and Clinical Practice Guideline

Having identified writing groups for each topic, the members designed questions to allow assessment of the literature in a manner that would

provide guidance for management of low grade gliomas. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of imaging assessment, diagnostic biopsy, surgical resection, tumor evaluation by standard neuropathology and molecular techniques, radiation therapy, chemotherapy, emerging therapies and treatment of recurrent or progressive low grade gliomas.

Guideline Panel Consensus

Multidisciplinary writing groups were created for each section based on author expertise, in order to address each of the disciplines and particular areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and scientific foundations for their specific section and discipline. Using this information, the writing groups then drafted the recommendations in answer to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire clinical guideline panel to allow for multidisciplinary feedback, discussion, and ultimately approval.

Rating Scheme for the Strength of the Recommendations

See the "Rating Scheme for the Strength of the Evidence" field.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Approval Process

The completed evidence-based clinical practice guidelines for the management of low grade gliomas were presented to the Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) for review. The reviewers for the Joint Guidelines Committee were vetted by the *Journal of Neuro-oncology* for suitability and expertise to serve as reviewers for the purposes of publication in that journal also. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in the *Journal of Neuro-oncology*.

The funding agencies (CNS Executive Committee and AANS/CNS Joint Tumor Section Executive Committee) were permitted to review these guidelines only after the Joint Guidelines Committee had completed its extensive review, critique and ultimate approval process; the funding groups then were limited to whether or not to endorse or reject this body of work but substantive changes were not allowed.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Two publications provide comparison of cytological/smear techniques and histological techniques, both highlighting the potential benefit of both frozen section histology in addition to cytological/smear preparations for diagnostic accuracy, providing class III evidence.
- One of the clear-cut benefits of IDH1 R132H antibody testing is the ability to sharpen the diagnostic boundaries between diffusely infiltrative low-grade diffuse astrocytomas and oligodendrogliomas, and other neoplastic and non-neoplastic mimics.

Potential Harms

False-positive and false-negative test results

Qualifying Statements

Qualifying Statements

The information in these guidelines reflects the current state of knowledge at the time of completion. Each section is designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Cahill DP, Sloan AE, Nahed BV, Aldape KD, Louis DN, Ryken TC, Kalkanis SN, Olson JJ. The role of neuropathology in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):531-49. [98 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Dec

Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

These guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) Guidelines Committee, with no funding from any outside commercial sources. Development of this set of evidence-based clinical practice guidelines was editorially independent from the funding agencies.

Guideline Committee

American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee

Low Grade Glioma Guidelines Task Force

Composition of Group That Authored the Guideline

Authors: Daniel P. Cahill, Department of Neurosurgery, Massachusetts General Hospital, Boston, MA, USA; Andrew E. Sloan, University Hospitals, Cleveland, OH, USA; Brian V. Nahed, Massachusetts General Hospital, Boston, MA, USA; Kenneth D. Aldape, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; David N. Louis, Department of Pathology, Massachusetts General Hospital, Boston, MA, USA; Timothy C. Ryken, Department of Neurosurgery, Kansas University Medical Center, Kansas City, KS, USA; Steven N. Kalkanis, Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA; Jeffrey J. Olson, Department of Neurosurgery, Emory Clinic, Atlanta, GA, USA

Financial Disclosures/Conflicts of Interest

Conflict of Interest

Low Grade Glioma Guidelines Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Disclosures

Dr. Kalkanis is a consultant for Arbor and Varian. Dr. Olson is a consultant for the American Cancer Society; has received research funding from the National Cancer Institute, Genentech, and Millennium; and has received investigational drug provision from Merck.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Neuro-Oncology Web site .

Availability of Companion Documents

The following are available:

- Rock J. Low grade glioma guidelines: foreword. J Neurooncol. 2015 Dec;125(3):447-8. Available from the Journal of Neuro-Oncology Web site .
- Olson JJ, Kalkanis SN, Ryken TC. Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J Neurooncol. 2015 Dec;125(3):449-56. Available from the Journal of Neuro-Oncology Web site .
- Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. [2 references]. Available from the Congress of Neurological Surgeons Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 7, 2016. The information was not verified by the guideline developer.

Copyright Statement

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Readers with questions regarding guideline content are directed to contact the guideline developer.